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ORIGINAL ARTICLE

Determine of the optimal number of cycles of docetaxel in the treatment of metastatic castration-resistant prostate cancer

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Abstract To determine the optimal number of cycles of docetaxel for metastatic castration-resistant prostate cancer, we retrospectively collected 73 patients receiving varying numbers of docetaxel plus prednisolone and analyzed the clinical outcomes including overall survival, prostate-specific antigen (PSA) response, and adverse events. The study included 33 patients receiving $\leq$ 10 cycles of docetaxel and 40 patients receiving $>$ 10 cycles. Patients receiving $>$ 10 cycles were younger than those who received $\leq$ 10 cycles. There was no statistical significant difference in overall survival between the two groups (log-rank test, $p = 0.75$). Adverse effects were more common among patients receiving $\geq$ 10 cycles of treatment. A PSA flare-up was observed among six patients (8.2%); the median duration of the PSA surge was 3 weeks (range, 3–12 weeks). The overall survival rates in patients with PSA flare-up were comparable with the patients having PSA response. We concluded that at least four cycles of docetaxel should be administered in metastatic castration-resistant prostate cancer patients in order not to cease treatment prematurely from potentially beneficial chemotherapy. However, administering $>$ 10 cycles does not result in any further improvement in survival and is associated with more adverse effects.
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Introduction

Castration-resistant prostate cancer (CRPC) generally has a poor prognosis and results in significant morbidity and mortality. Chemotherapy has been the first-line treatment for metastatic CRPC (mCRPC) since 2004, and docetaxel-based regimens have been shown to improve both patient symptoms and survival [1–3]. Docetaxel plus prednisolone (DP) administration every 3 weeks is now established as a first-line therapy for CRPC, and results in the best overall survival (OS) [1,3]. Between 2004 and 2010, there were no second-line agents available that could improve survival after docetaxel failure. Moreover, the optimal number of treatment cycles when administering docetaxel has always been disputed. Some studies reported that a considerable portion of patients experienced an initial prostate-specific antigen (PSA) surge without clinical disease or symptom progression, and then subsequently showed PSA decline, called PSA flare phenomenon. All studies showed that PSA flare-up did not have a negative effect on survival compared with the initial PSA response group [4–6], which made it unnecessary to stop chemotherapy prematurely only due to initial PSA increasing. Furthermore, in the TAX-327 [3] and SWOG 99-16 [1] studies, up to 11 or 12 cycles of docetaxel-based chemotherapy were administered, after which disease progression, severe adverse events, or death occurred. Therefore, a treatment regimen of approximately 10 cycles became accepted clinical practice. However, the potential advantages or disadvantages of extending treatment beyond 10 cycles remain unknown. After 2011, agents that extended survival for patients with CRPC were developed [7,8], and it has therefore become more important to determine the optimal duration of docetaxel treatment and hence to better understand when second-line therapy with these new agents should be initiated. The aim of this study was to determine the optimal number of treatment cycles by analyzing the survival outcome, PSA response, and adverse events of patients receiving DP every 3 weeks; to identify the benefits of extending DP treatment beyond 10 cycles; and to evaluate the impact of a PSA flare-up.

Materials and methods

Through retrospective chart review (Chang Gung Institutional Review Board approved) we selected patients with mCRPC who had received three cycles or more than of docetaxel, and had image-proved bone, lymph node, or visceral metastases. Eligible patients had an Eastern Cooperative Oncology Group performance status of 0–2 (patients with a performance status of 3 due to bone pain were also eligible). Premedication with 8-mg dexamethasone followed by docetaxel (Taxotere, Aventis) at 75 mg/m^2 was administered, together with oral prednisolone twice daily, in accordance with the TAX-327 regimen [1]. The dose was reduced to 60 mg/m^2 if the serum level of alanine aminotransferase (AST) and aspartate aminotransferase (ALT) increased to 1.5–3.5 times the upper limit or hyperbilirubinemia. In addition, if there had been febrile neutropenia in a previous cycle, treatment was delayed by up to 3 weeks or until the neutrophil count exceeded 1500/mm^3. Chemical androgen deprivation therapy was continued during chemotherapy for patients who had not undergone an orchiectomy. Bisphosphonate treatment was also prescribed for patients with significant bone pain associated with bony metastases.

Follow-up and outcome

Blood tests for the assessment of PSA, complete blood count, renal function, and liver function were repeated every 3 weeks on Day 1 before chemotherapy. The PSA response was categorized by the magnitude of the change in PSA level. The responder group was defined by a reduction of serum PSA level by at least 50% from baseline, whereas the Nonresponder group was defined by PSA progression. Patients who did not fit either criterion were included in the Stable group. Patients who initially had a rising PSA value without clinical disease progression, and subsequently showed a PSA decline of $>$ 50%, were categorized as being in the PSA flare-up group, in accordance with the Olbert et al's [5] and Nelius et al's series [4]. In the subanalysis of patients receiving $>$ 10 cycles of therapy, the baseline PSA was defined as the level on the first of the 11th cycle of chemotherapy. Treatment was continued until serious or intolerable adverse events occurred. Adverse events were classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4. Serious adverse events included intolerable peripheral sensory neuropathy and other fatal conditions such as sepsis or impending hepatic failure.

Statistical analysis

A Kaplan–Meier plot was used to estimate the OS probability between treatment groups. Log-rank test and Cox's proportional-hazards model were used to evaluate the significance of additional cycles of treatment. Additionally, the PSA response after chemotherapy was examined as a secondary outcome. The Fisher's exact test, Pearson's Chi-square test, and two-tailed independent *t*-test were carried out with the SPSS software, version 17.0 to identify a relationship between demographic and clinical variables, occurrence of adverse events, and PSA response.

Results

Between October 2005 and May 2012, a total of 92 patients received docetaxel chemotherapy in our institute. After excluding the patients who were administered $<$ 3 cycles of chemotherapy, 73 patients met the eligible criteria and their data were collected for analysis. There were 33 patients receiving $\leq$ 10 cycles and 40 patients receiving $>$ 10 cycles (Table 1). Compared with the patients who received $\leq$ 10 cycles, patients who received $>$ 10 cycles were on average, younger (70.0 $\pm$ 8.1 vs. 74.4 $\pm$ 7.6 years; $p = 0.019$) and had a longer follow-up (22.6 $\pm$ 10.3 vs. 14.6 $\pm$ 14.4 months; $p = 0.008$). The baseline PSA was not significantly different between the groups (544.6 $\pm$ 1038.3 vs. 446.1 $\pm$ 753.8; $p = 0.417$), and neither were other baseline characteristics irrespective of prior radiotherapy, the extent of distant metastases, and the use of

Table 1 Baseline patient characteristics.

	≤10 cycles	>10 cycles	*p*
Patient no.	33	40	
Baseline characteristics			
Mean age (y)	74.4 ± 7.6	70.0 ± 8.1	0.019
Follow up duration (mo)	14.6 ± 14.4	22.6 ± 10.3	0.008
No. of cycles (range)	6.6 ± 2.3 (3–10)	19.3 ± 7.8 (11–39)	0.000
ECOG performance 0–1, *n* (%)	30 (90.1)	35 (87.5)	0.643
Baseline PSA (ng/mL)	544.6 ± 1038.3	446.1 ± 753.8	0.417
Extent of disease, *n* (%)			
Bone metastases	32 (97)	37 (92.5)	0.622
Lymph node metastases	7 (21.2)	15 (37.5)	0.131
Visceral metastases[a]	2 (6.1)	3 (7.5)	1.0
Prior radiotherapy, *n* (%)	4 (12.1)	7 (17.5)	0.523
Concomitant bisphosphonate, number (*n*)	22	24	0.557

ECOG = Eastern Cooperative Oncology Group; PSA = prostate-specific antigen.
[a] Liver or lung metastases.

concomitant bisphosphonate. The average docetaxel administration was 6.6 cycles and 19.3 cycles (range, 11–39 cycles, $p < 0.001$) in the patients receiving ≤ 10 cycles and > 10 cycles, respectively. The median survival in patients receiving ≤ 10 cycles and > 10 cycles was 13.4 months and 22.7 months, respectively, but there was no significant difference in OS probability between the two groups (log-rank test, $p = 0.75$; Figure 1). Even after adjusting the factor of age by Cox regression model, there was no difference in both groups ($p = 0.71$). With respect to the initial PSA response, 39.4% and 35% of patients' PSA decline of > 50% from baseline in the groups receiving ≤ 10 cycles and > 10 cycles, respectively ($p = 0.752$; Table 2). Comparing the PSA response after the 11th cycle of chemotherapy with initial PSA response in ≤ 10 cycles group, there was only 17.5% patients having PSA decline > 50% but there was no statistical difference ($p = 0.109$).

The adverse effects after docetaxel treatment are listed in Table 3. There were more adverse events involving the hepatobiliary system together with a higher incidence of abnormal AST and ALT in patients who received > 10 cycles of therapy ($p = 0.001$ and $p = 0.014$). One patient who received 38 cycles of docetaxel suffered fatal hepatic failure, which resulted in death. Peripheral sensory neuropathy (≥ Grade 2) was also prominent in patients receiving > 10 cycles of treatment ($p = 0.009$). Among all 73 patients, 36 (49.3%) achieved a 50% PSA decline, 23 (31.5%) achieved PSA stabilization, and 14 (19.2%) had PSA progression. In the responder group, six patients (8.2%) had PSA flare-up without evidence of clinical deterioration or disease progression. The median duration of the PSA surge was 3 weeks (range, 3–12 weeks) and the median PSA surge was 16.9% (range, 5.8–100%). The median survival was 37.1 months, 26.8 months, and 18.8 months in the PSA flare-up, Responder, and Progression groups, respectively. The OS in the Responder group was better than patients in the Progression group (Figure 2A; $p = 0.036$) and there was no difference in OS between the Responder and PSA flare-up groups ($p = 0.977$; Figure 2B).

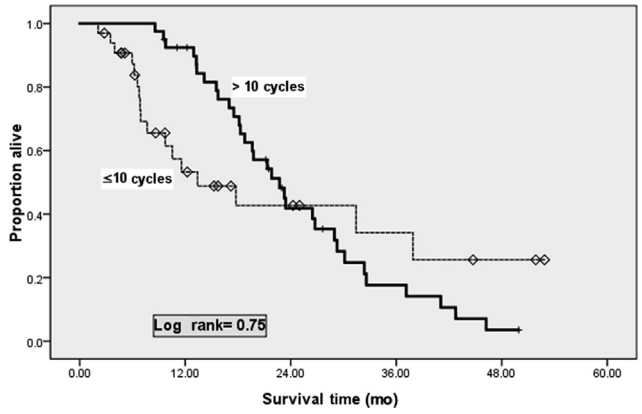

Figure 1. Kaplan–Meier curve of overall survival for patients receiving ≤ 10 cycles and > 10 cycles of treatment.

Discussion

DP every 3 weeks has been established as first-line chemotherapy for mCRPC, giving a modest 2–3-month survival advantage over conventional palliative chemotherapy regimen in combination with prednisone according to the TAX-327 study and a subsequent, updated report [1,3]. However, the optimal number of cycles remains unclear. It is important to identify at which stage second-line therapy should be initiated because new, second-line agents also provide a substantial survival benefit [7,8]. The original design of the TAX-327 and SWOG 99-16 studies on docetaxel treatment for mCRPC specified a maximum of 12 cycles due to toxicity concerns, and as a result little is known regarding the outcomes of treating with > 10 cycles. Prior to 2012, there was no therapeutic agent available after docetaxel failure in our institute, and as a result, 40 patients (54.8%) received > 10 cycles of docetaxel; the treatment only ended when serious or intolerable adverse events occurred. Patients receiving > 10 cycles were on average younger, possibly because this meant they could tolerate chemotherapy better. The survival benefit was good before 18 months, but there was no significant benefit

Table 2 Prostate-specific antigen (PSA) response in patients receiving ≤ 10 cycles or > 10 cycles of therapy.

	≤10 cycles	>10 cycles (after first cycle)	>10 cycles (after 11th cycle)	*p*
Patient (*n*)	33	40	40	
PSA response, *n* (%)				0.752[a]
PSA decline <50%	12 (36.4)	18 (45)	21 (52.5)	
PSA progression	8 (24.2)	8 (20)	12 (30)	
PSA decline ≥50%	13 (39.4)	14 (35)	7 (17.5)	

[a] Between ≤ 10 cycles group and > 10 cycles (initial response after first cycle).

of extending treatment beyond 10 cycles during a longer follow-up period. In the TAX-327 and SWOG 99-16 trials, chemotherapy was withdrawn if there was disease progression or an unacceptable adverse event. Another randomized, phase-2 trial conducted by Ascenta Therapeutics (CS-205) allowed for up to 17 cycles of DP or a placebo, and compared its use in combination with AT-101, a B-cell lymphoma-2 antagonist [9]. A retrospective hypothesis-generating analysis compared the TAX-327 and CS-205 studies and also concluded that there was no survival benefit in men with mCRPC who received > 10 cycles of docetaxel treatment [10].

Table 3 Adverse events.

	≤10 cycles (*n* = 33)	>10 cycles (*n* = 40)	*p*
Hematologic system, *n* (%)			
Anemia ≥ Grade 3	18 (54.5)	22 (55)	0.969
Thrombocytopenia, platelets < 10^5/mm^3	12 (36.4)	18 (45)	0.455
Neutropenia, ANC < 1500/mm^3	8 (24.2)	13 (32.5)	0.438
Hepatobiliary system, *n* (%)			
Abnormal AST	19 (57.6)	36 (90)	0.001
Abnormal ALT	8 (24.2)	21 (52.5)	0.014
Abnormal total bilirubin	7 (21.2)	11 (27.5)	0.535
Hepatic failure ≥ Grade 2	0 (0)	1 (2.5)	1.0[a]
Gastrointestinal system, *n* (%)			
Diarrhea ≥ Grade 2	3 (9.1)	6 (15.0)	0.499[a]
Nausea/vomiting ≥ Grade 2	9 (27.3)	18 (45.0)	0.118
Stomatitis ≥ Grade	3 (9.1)	3 (7.5)	1.0[a]
Others, *n* (%)			
Fatigue ≥ Grade 2	9 (27.3)	18 (45.0)	0.118
Alopecia ≥ Grade 2	5 (15.2)	14 (35.0)	0.054
Peripheral sensory neuropathy ≥ Grade 2	1 (3)	10 (25)	0.009
Treatment related death	0 (0)	1 (2.5)	1.0[a]

ALT = aspartate aminotransferase; ANC = absolute neutrophil count; AST = alanine aminotransferase.
[a] Fisher's exact test.

Generally, systemic cytotoxic chemotherapy for advanced cancer is administered for no more than six cycles due to toxicity concerns. Docetaxel is mainly metabolized in the liver and has the potential to cause hepatocyte damage and even severe fulminant hepatocellular necrosis [11]. Elevated liver enzyme levels (AST and ALT) indicate the severity of hepatocyte damage. In this study, there were significantly more patients with abnormal AST and ALT in the group treated with > 10 cycles for docetaxel, and the severity of liver damage also increased. Peripheral sensory neuropathy also occurred more frequently in patients receiving an extended course of treatment due to the higher cumulative dosage. Although some experts advocated intermittent chemotherapy to reduce toxicity [12–16], the impact of this on survival was unclear. It is necessary to optimize the maximal number of docetaxel treatment cycles in order to prevent bone marrow exhaustion and other adverse events so that the patient can benefit from second-line therapy.

Other than the maximal number of docetaxel therapy cycles, we also addressed the minimum number of cycles

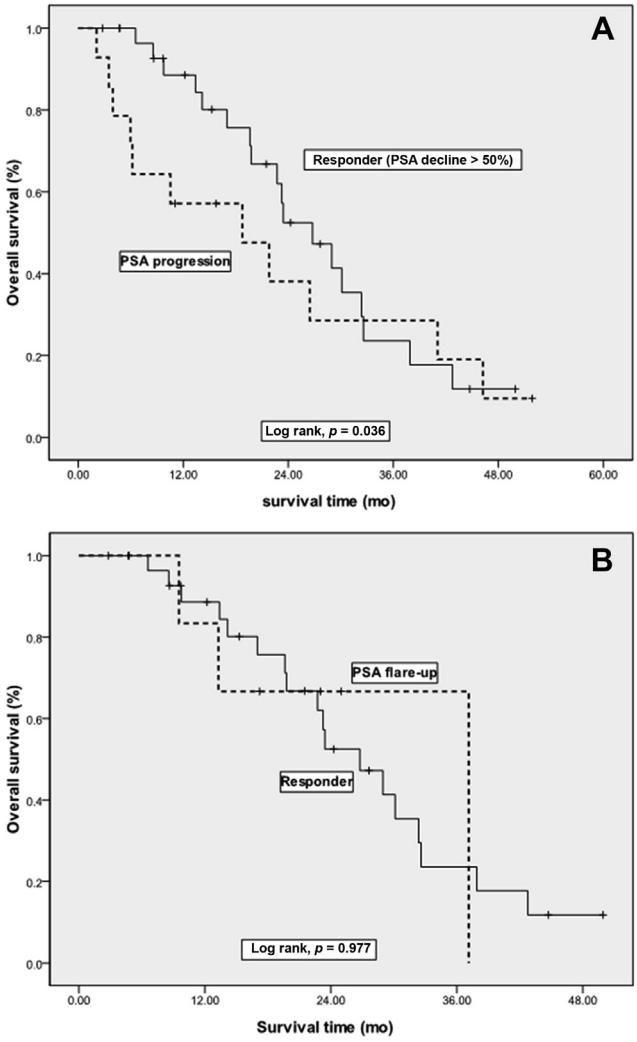

Figure 2. Kaplan–Meier curve of overall survival between: (A) prostate-specific antigen (PSA) progression and responder; and (B) PSA flare-up and responder.

that could be effective. An initial PSA surge before a therapeutic response is a known phenomenon androgen-deprivation therapy in hormone sensitive prostate cancer. This "flare" has also been reported in patients with docetaxel [4—6]. Due to a number of patients experiencing an initial PSA flare-up phenomenon during docetaxel chemotherapy (ranging from 10% to 18%) [4—6,17,18], and as previous studies have shown this does not have a negative impact on survival [4—6], it means some patients would present with initial PSA elevation possibly followed by a subsequent response and had the same survival benefit with the PSA response group. Stopping chemotherapy prematurely (before the 1st 12 weeks or four cycles) may allow this group of patients to lose the chance of receiving survival benefits. Physicians should not cease chemotherapy based only on an initial rise in PSA. Possible reasons for a PSA flare-up include its release into the circulation from acute tumor lysis, transactivation of mutated androgen receptors by the estramustine component, the effects of premedication with dexamethasone, and the increased differentiation of cancer stem precursors [19,20]. We found that the median duration of the PSA surge was 3 weeks and the range was 3—12 weeks. At least four cycles of treatment were advised, unless there were intolerable side effects or clinical disease progression, in order to prevent premature exclusion of patients from a potentially beneficial chemotherapy regimen. The Prostate Cancer Clinical Trials Working Group-2 criteria also recommended at least four cycles before evaluating the response due to this concern [21]. We found no survival benefit with administering $>$ 10 cycles, which was related to an increased number of adverse events. Therefore, proceeding to second-line therapy or enrollment in another clinical trial should be considered after approximately 10 cycles of treatment, regardless of the PSA response. To the best of our knowledge, the number of patients receiving $>$ 10 cycles exceeds that in other reports. We also suggest that the bias related to treatment strategy can be minimized in a report from a single institute. However, this study was limited due to its retrospective nature, and potential bias due to the lack of baseline equivalence in the patients receiving different numbers of treatment cycles and variation of follow-up duration. A further randomized controlled trial is necessary to compare extended doses of docetaxel with other potential cytotoxic or biologic therapies.

According this study, it suggests at least four cycles of docetaxel for patients with mCRPC in order not to cease treatment prematurely from potentially effective chemotherapy. Administering $>$ 10 cycles of DP for 3 weeks does not extend survival and results in more adverse effects. Proceeding to a second-line therapy should not be retarded by first-line docetaxel, especially when exceeding 10 cycles.

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